Research Square

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Gestational age-specific normative values and determinants of serum progesterone through the first trimester of pregnancy

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Research article

Keywords: progesterone, normative values, reference range, first trimester, luteal placental, Singapore

Posted Date: April 2nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-20078/v1

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Abstract

BACKGROUND: Progesterone is a steroid hormone that is critical for implantation and maintenance of pregnancy, with low levels being associated with a significantly higher miscarriage risk. Despite its pivotal role, especially during early pregnancy, reference range studies of serum progesterone are predominantly trimester-specific with wide ranges that are not clinically useful. Although it is established that serum progesterone exhibits an overall increasing trend during pregnancy, little is known about its trajectory during early pregnancy. We sought to find the gestational age-specific normative values and trajectory of serum progesterone, and its associated maternal and fetal factors, during the first trimester of a viable low-risk pregnancy.

METHODS: A prospective cohort study was conducted at KK Women's and Children's Hospital from 1 April 2012 to 31 January 2018, recruiting 590 women with a single intrauterine low-risk pregnancy, presenting at antenatal clinics between gestational weeks 5 to 12. Gestational age-specific normative values and trajectory of serum progesterone were determined via quantile regression. Maternal and fetal characteristics that influence normative values of serum progesterone were determined via univariable analyses followed by multivariable regression.

RESULTS: Serum progesterone showed an increasing trend during the first trimester of a viable low-risk pregnancy, with a transient decline between gestational weeks 6 to 8 corresponding to the luteal-placental shift. Lowest levels were seen at week 7 (mean serum progesterone of 75.0 nmol/L at week 5 versus 63.4 nmol/L at week 7, p=0.029; 63.4 nmol/L at week 7 versus 78.0 nmol/L at week 9, p<0.001). In a multivariable logistic regression, gestational age, maternal age, maternal body mass index at presentation, parity and fetal gender were found to be associated with progesterone levels, explaining 18.8% of the variability.

CONCLUSIONS: Our study described the gestational age-specific normative values and increasing trajectory of serum progesterone, with a physiological decline during weeks 6 to 8 of gestation. This forms the basis for future work on pathological levels of serum progesterone that may lead to miscarriage. Larger studies are also required to investigate the need for normative values to be developed, and personalized to account for maternal BMI, parity and fetal gender.

Background

Progesterone is a steroid hormone critical for the establishment and maintenance of early pregnancy. It prepares the endometrium for blastocyst implantation, sustains decidualization, reduces uterine contractility and promotes maternal immune tolerance to the fetal semi-allograft (2)1. Many studies have reported a significantly higher risk of adverse pregnancy outcomes in women with low serum progesterone during pregnancy (2–5). Excess serum progesterone, on the other hand, was reported to significantly suppress expression levels of decidualization markers in a dose-dependent manner and compromise embryo decidualization (6).

In order to meaningfully interpret measured values of serum progesterone during early pregnancy, it is important to first establish gestational age-specific normative serum progesterone values to form a basis for reference and comparison. However, despite its pivotal role during early pregnancy, reference range studies of serum progesterone are predominantly trimester-specific and have wide ranges that are not clinically useful (7, 8).

Furthermore, although progesterone has been reported to exhibit an overall increasing trend during pregnancy (3, 9), little is known about its trajectory during early pregnancy. Progesterone is secreted primarily by the corpus luteum, with the placenta eventually taking over if pregnancy occurs. This transition in progesterone production from the corpus luteum to placenta is known as the luteal-placental shift, and it occurs between weeks 6 to 8 of gestation. This period has been determined by earlier studies where corpus luteum removal prior to week 7 of gestation resulted in an immediate fall in serum progesterone levels and eventual miscarriage, while corpus luteum removal after week 9 of gestation resulted in pregnancy survival (10, 11). A few studies have suggested a trajectory where progesterone level starts decreasing around gestational week 5, reaching a nadir between weeks 6 to 8 corresponding to the luteal-placental shift, before increasing thereafter (12, 13). However, these studies are limited by small sample sizes as well as generalizability, for example by including only anovulatory women who conceived after induction of ovulation with gonadotrophins.

The primary aim of this study was to establish gestational age-specific normative values and trajectory of serum progesterone in the first trimester of a viable low-risk pregnancy. The secondary aim was to determine maternal and fetal factors that were associated with serum progesterone levels. Establishing such normative values in early pregnancy has far reaching implications. Patients whose serum progesterone lies beyond the normal range would be brought to the attention of clinicians, especially those with extremely low levels, representing a high-risk group with necessity for closer monitoring or medical intervention.

Methods

Study Design

This prospective cohort study was conducted from 1 April 2012 to 31 January 2018 at KK Women's and Children's Hospital (KKH), the largest maternity hospital in Singapore.

Study Participants and Eligibility

Study participants were pregnant women aged 21 and above presenting for routine antenatal screening at KKH clinics. Inclusion criteria were a single intrauterine pregnancy between weeks 5 to 12 of gestation, confirmed and dated via ultrasonography, with no pregnancy-related per vagina bleeding. Gestation week was defined as gestation week 5 (week 5.0 to 5.9), gestation week 6 (week 6.0 to 6.9) and so on. Women

with multiple gestations, previous episodes of pregnancy-related per vagina bleeding or those treated with progesterone in the current pregnancy, women diagnosed with an inevitable miscarriage, missed miscarriage, blighted ovum or planned pregnancy termination were excluded. To restrict the analysis to viable pregnancies, study participants with spontaneous miscarriage by week 16 of gestation were also excluded. Pregnancy outcome was determined via a phone call to study participants at week 16 of gestation and clinically confirmed to verify pregnancy status.

Ethical Approval

This study was reviewed and approved by the Singapore Centralized Institutional Review Board (CIRB 2016/3093). Written informed consent was obtained from all participants before participating in this study.

Serum Measurements

Serum progesterone level was obtained from blood samples of eligible study participants taken at presentation. Individual blood sample was collected in plain tubes and centrifuged for 10 minutes at 3000 g within 2 hours of collection. Serum progesterone level was subsequently measured in the KKH clinical laboratory using a commercial ARCHITECT progesterone kit (Abbott, Ireland), according to manufacturer's instructions.

Maternal and Fetal Characteristics

Information on pregnancy characteristics were obtained to determine maternal and / or fetal characteristics that influence normative values of serum progesterone in the first trimester of a viable low-risk pregnancy. Information on maternal characteristics were obtained from questionnaires administered by an investigator either in English or Chinese, while information on the fetal characteristics were obtained either from clinical notes or during subsequent follow-up visits. Prior to the start of patient recruitment, a literature review was conducted to identify potential pregnancy characteristics that may influence serum progesterone levels. These include gestational age, maternal characteristics such as Body Mass Index (BMI), age, parity, smoking status and ethnicity, as well as fetal characteristics such as gender. Maternal BMI at presentation was taken as a proxy for pre-pregnancy BMI, calculated as weight (14) / height $(m)^2$ and stratified according to Asian-specific World Health Organization definitions of underweight (< 18.5 kg/m^2), normal (18.5 to < 23 kg/m^2), overweight (23 to < 27.5 kg/m^2) and obese (≥ 27.5 kg/m^2) (1). Parity was defined as either nulliparous women who had never given birth, or parous women who had at least one full-term pregnancy previously.

Statistical Analysis

SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) was used for statistical computation. Quantile regression was performed to construct the 2.5th, 10th, 50th, 90th and 97.5th percentiles model of serum progesterone level versus week of gestation. Restricted cubic splines with knots at 6, 8 and 10 weeks were used to describe the shape of the serum progesterone trajectory across gestation. Analysis of variance using least squares means was then used to test for significance of the serum progesterone distributions between individual gestational weeks.

Associations between maternal or fetal characteristics and log-transformed values of serum progesterone levels were analyzed using univariate analysis and a subsequent multivariable linear regression was performed to adjust for confounding factors.

In all analyses, a p-value of < 0.05 was considered statistically significant.

Results

The study population analyzed comprised of 590 pregnant women (Figure 1), with descriptive characteristics as shown in Table 1. Mean maternal age was 30.7 years, and the median gestational age at recruitment was 8.7 weeks. Majority of the participants were of Chinese ethnicity (48.8%), and of normal BMI, between 18.5 to <23 kg/m^2 (48.0%). Amongst the participants with information at delivery, 49.8% had a female baby and 50.2% had a male baby (missing data n = 134).

Normative values and trajectory of serum progesterone

Gestational age-specific normative values and trajectory of serum progesterone were established (Table 2 and Figure 2). Serum progesterone level started to decline after gestation week 5, reaching a nadir at week 7 (mean serum progesterone in week 5 = 75.0 nmol/L, compared to 66.9 nmol/L in week 6 ($p = 0.057$), and 63.4 nmol/L in week 7 ($p = 0.029$)). It increases thereafter from gestation weeks 7 to 9 (mean serum progesterone in week 7 = 63.4 nmol/L, compared to 67.7 nmol/L in week 8 ($p = 0.374$) and 78.9 nmol/L in week 9 ($p < 0.001$).

Determinants of serum progesterone

Maternal and/or fetal characteristics that may potentially influence serum progesterone levels were investigated. Significant associations were shown in Table 3 and Figure 3. Using a multivariable logistic regression, gestational age, maternal age, maternal BMI at presentation, parity and fetal gender were

found to be the main determinants of serum progesterone levels at presentation, explaining 18.8% of the variability.

Women who were obese (BMI ≥ 27.5 kg/m^2) had significantly lower serum progesterone levels on average as compared to those with normal BMI (mean serum progesterone difference of 17.1 ± 3.0 nmol/L, $p < 0.001$). Nulliparous women had higher serum progesterone levels on average as compared to parous women (5.4 ± 2.2 nmol/L, $p = 0.011$). Higher serum progesterone levels were also seen in women expecting a female baby as compared to those expecting a male baby (4.5 ± 2.3 nmol/L, $p = 0.032$). Maternal age showed a small but significant positive correlation with serum progesterone levels (0.092, $p = 0.025$).

Discussion

We conducted a prospective cohort study to determine gestation age-specific normative values and determinants of serum progesterone through the first trimester of a viable low-risk pregnancy. To the best of our knowledge, this is one of the first studies to determine normative values of serum progesterone on a gestation week-by-week basis in the first trimester, which is the most crucial stage of pregnancy. Having established a reference range, clinicians would be able to better identify women whose serum progesterone level deviate from the normal range, and correlate to clinical outcomes in future population-based studies. If abnormal gestational-age specific serum progesterone correlates to pathological outcomes, this will pave the way for personalized medicine with closer monitoring and medical interventions for this group of women.

Even though serum progesterone is known to exhibit an overall increasing trend during pregnancy, we showed that it also follows an interesting trajectory of transient decline between weeks 6 to 8 of gestation with significantly lower levels seen in week 7. This decline corresponds to the period of luteal-placental shift. Progesterone is secreted by the corpus luteum, which only lasts for 14 days if a pregnancy does not occur. In early pregnancy, beta human chorionic gonadotropin (β-hCG) secreted by syncytiotrophoblasts maintains the corpus luteum, allowing it to produce progesterone until the placenta takes over its function at 7 to 9 weeks of gestation. Earlier studies defined this period of luteal-placental shift by demonstrating that lutectomy performed prior to week 7 resulted in an immediate progesterone drop with eventual abortion whereas lutectomy after week 9 resulted in pregnancy survival (10, 11). Furthermore, our data adds further evidence to studies by *Yoshimi* and *Jarvela,*in which a similar progesterone trajectory was described, albeit in a small cohort of 9 and 20 women respectively (12, 13).

Luteal phase deficiency (LPD) is a condition of insufficient progesterone to maintain a normal secretory endometrium and allow for normal embryo implantation and growth (15). This is one of many etiologies associated with early pregnancy loss. Two mechanisms have been proposed for LPD. The first and likely more common cause relates to the impaired function of the corpus luteum, resulting in insufficient progesterone and estradiol secretion. This impaired function can be the result of improper development of the dominant follicle destined to become the corpus luteum or aberrant stimulation of a normally

developed follicle, leading to deficiencies in progesterone production. The second mechanism suggests an inability of the endometrium to mount a proper response to appropriate estradiol and progesterone exposure. In our study, it is worth highlighting that even though there was a transient decline in serum progesterone levels, it did not translate to adverse pregnancy outcomes such as miscarriages. Our study highlighted the physiological decline in serum progesterone between weeks 6 to 8 in a normal low-risk cohort. Further work needs to be done to investigate pathological changes in serum progesterone during this crucial period in order to allow clinicians to better characterize LPD, which was previously impossible without a normal reference range.

We identified five main determinants of serum progesterone in the first trimester of a viable pregnancy—gestation age, maternal BMI, parity, fetal gender and maternal age. Maternal BMI was found to be inversely correlated with serum progesterone, and that is consistent with many previous studies. This has been thought to be attributed to early biochemical alterations associated with obesity, leading to lower progesterone levels (16). Reduced pulsatile luteinizing hormone amplitude and urine progesterone metabolites were seen in obese women as compared to those with normal body weight (17). Adipocytokines have also been shown to negatively affect function of the corpus luteum (18). Moreover, since progesterone is a lipid-soluble hormone, this equates to a higher volume of distribution, hence resulting in lower circulating serum progesterone levels.

Evidence regarding parity and its association with serum progesterone have been inconsistent, with most studies showing no significant differences in serum progesterone levels between the first and subsequent pregnancies (19). In our study, we found that women who previously had at least one full-term pregnancy had lower serum progesterone levels as compared to primiparous women (mean serum progesterone difference of 5.4 ± 2.2 nmol/L, $p = 0.011$). This is in line with studies exploring long-term effects of a first pregnancy on the hormonal environment. In these studies, pregnancy-related hormones such as β-hCG (20–22) and estradiol (23), have been observed to decrease in pregnancies following the first child birth. Reduced β-hCG levels in turn leads to lower serum progesterone, as β-hCG is involved in sustaining the corpus luteum and progesterone production before the placenta takes over. The mechanism underlying this decline in certain pregnancy-related hormones is still largely unknown. It is postulated that prior full-term pregnancies may induce alterations in a woman's hormonal milieu, such as altered maternal hormone metabolism, increased levels of binding proteins leading to reduced hormone bioavailability and modulation of hormone receptor expression (20). Future studies can seek to delve further into this concept of hormonal alterations after a prior pregnancy, with possible implications on hormonal profiles in the critical first trimester period.

Previous studies investigating serum progesterone and fetal gender have also been inconclusive, reporting either similar progesterone levels (22) or lower serum progesterone in women expecting a female baby (24). In our study, we observed that women with a female fetus had higher serum progesterone compared to those with a male fetus (mean serum progesterone difference of 4.5 ± 2.3 nmol/L, $p = 0.032$). Higher serum β-hCG levels have been reported in women with a female fetus (21, 25, 26), detectable as early as week 5 of gestation (27). This is thought to be mediated by gender-specific

differences in placental gene expression (28, 29), whereby X-chromosome genes could become over-expressed by the placenta of a female baby should they fail to undergo proper inactivation (27, 30).

The main strength of our study is that this is one of the first and largest population-based studies to determine gestation age-specific normative range of serum progesterone through the first trimester of viable low-risk pregnancy, which is the most crucial stage of a pregnancy. Furthermore, we were able to plot the trajectory of first trimester serum progesterone in this cohort. The main limitation of this study is that the serum progesterone levels of women were measured at presentation across gestation, with inherent biological variability from woman to woman, instead of through a serial examination of serum progesterone in the same woman every week. However, adopting the latter study design would require study participants to return for weekly follow-ups and have blood tests performed at every visit, which would decrease compliance and increase dropout rates, and more importantly may not be ethically feasible.

Conclusion

This is one of the largest cohort studies to describe the normative serum progesterone values across the first trimester of a low-risk viable pregnancy. We have demonstrated the physiological decline in serum progesterone corresponding to a luteal-placental shift between 6 to 8 weeks of gestation with a nadir at week 7. This study will form the basis for future work on pathological levels of serum progesterone that translates to adverse clinical outcomes, such as threatened or spontaneous miscarriage. Maternal BMI, parity and fetal gender were also shown to be associated with serum progesterone levels. Larger studies are required to investigate the need for normative values developed specifically for these groups of women.

Abbreviations

β-hCG: Beta Human Chorionic Gonadotropin; BMI: Body Mass Index; LPD: Luteal Phase Deficiency

Declartions

Ethics approval and consent to participate

This study was reviewed and approved by the Singapore Centralized Institutional Review Board (CIRB 2016/3093). Written informed consent was obtained from all participants before participating in this study.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available due to confidentiality consent of the study but can be obtained from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study is funded by the Ministry of Health Industry Alignment Fund Category 1, Singapore (MOHIAFCat1–11010).

Authors' contributions

C. W. K.: contributed to interpretation of the data, revised the manuscript for important intellectual content and was the main co-first author; X. Z.: contributed to the development of the study design, contributed in data extraction, performed the statistical analyses and interpretation of the data, drafted the manuscript and was the main co-first author; T.Ø.: contributed to development of the study design and analysis strategy, and revised the manuscript for important intellectual content; J. C. A.: performed the statistical analyses, contributed to the interpretation of the data and provided editorial guidance; V. R. Y. Z.: contributed to manuscript writing, revision and editorial support; T. C. T.: contributed to development of the study design and analysis strategy, provided editorial guidance and had overall supervision of the study; All the authors approved the final manuscript for submission.

Acknowledgements

The authors will like to thank Ms Trish Koon, Ms Doris Ong and Ms Erica Nuriyah Fadziulah for their assistance in patient recruitment. We wish to thank all the families who participated in our research and all the dedicated staff from participating departments.

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Tables

Due to technical limitations, all tables are only available for download from the Supplementary Files section.

Figures

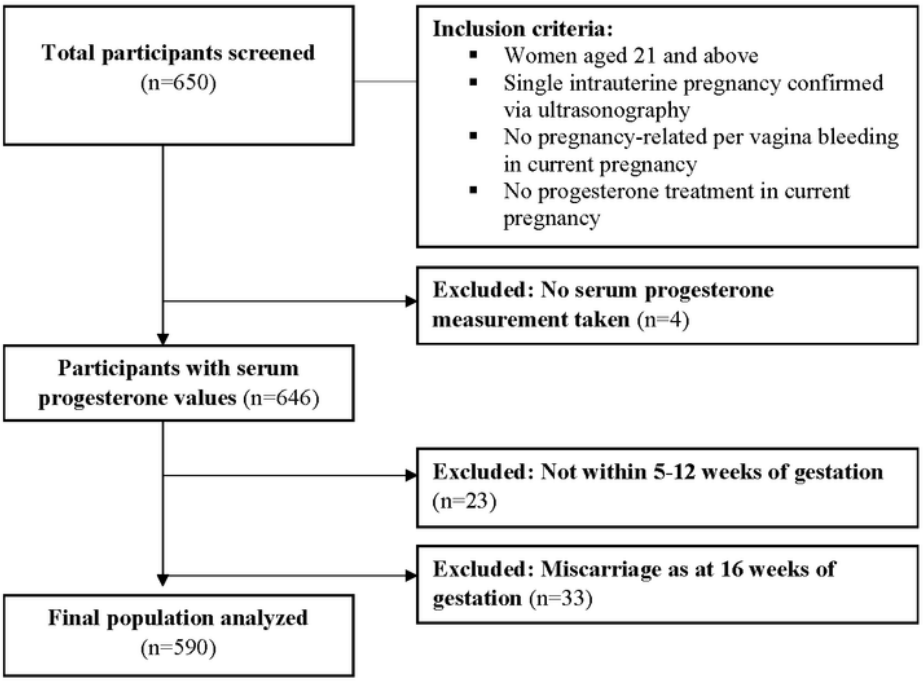

Figure 1

Consort diagram of study participants used to establish normative values of serum progesterone

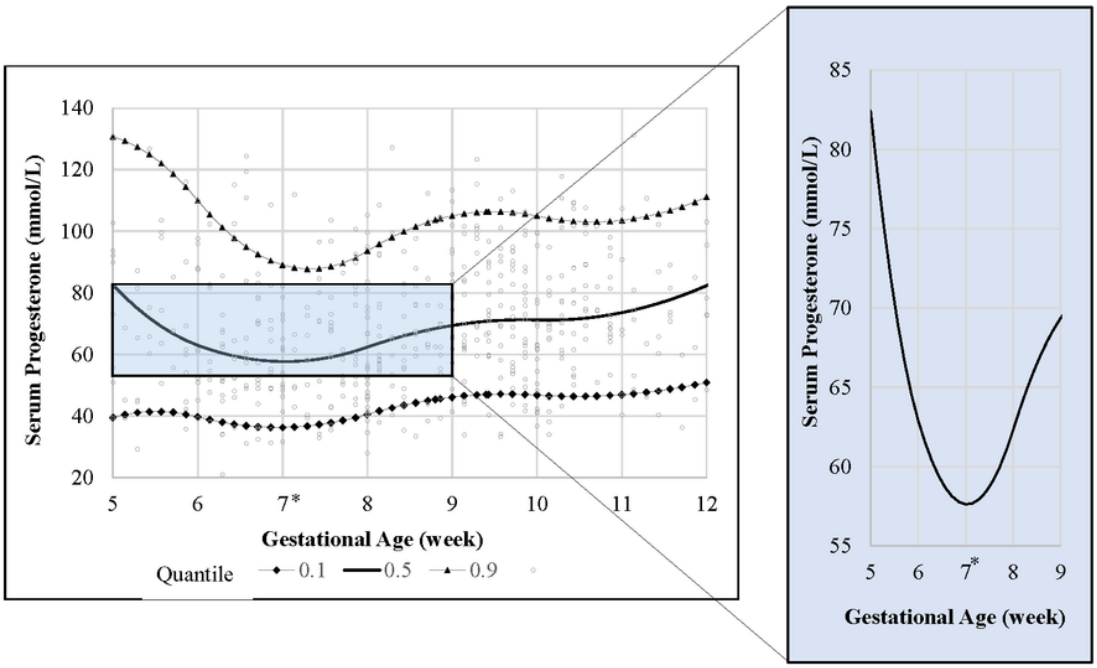

Figure 2

Gestational age-specific 10th, 50th and 90th percentile normative values of serum progesterone. Restricted cubic splines with knots at 6, 8 and 10 weeks were used to describe the shape of the serum progesterone trajectory across gestation. *Mean serum progesterone at gestational week 7 (63.4 nmol/L) compared against week 5 (75.0 nmol/L, p=0.029), week 6 (66.9 nmol/L, p=0.694), week 8 (67.7 nmol/L, p=0.374) and week 9 (78.0 nmol/L, p<0.001).

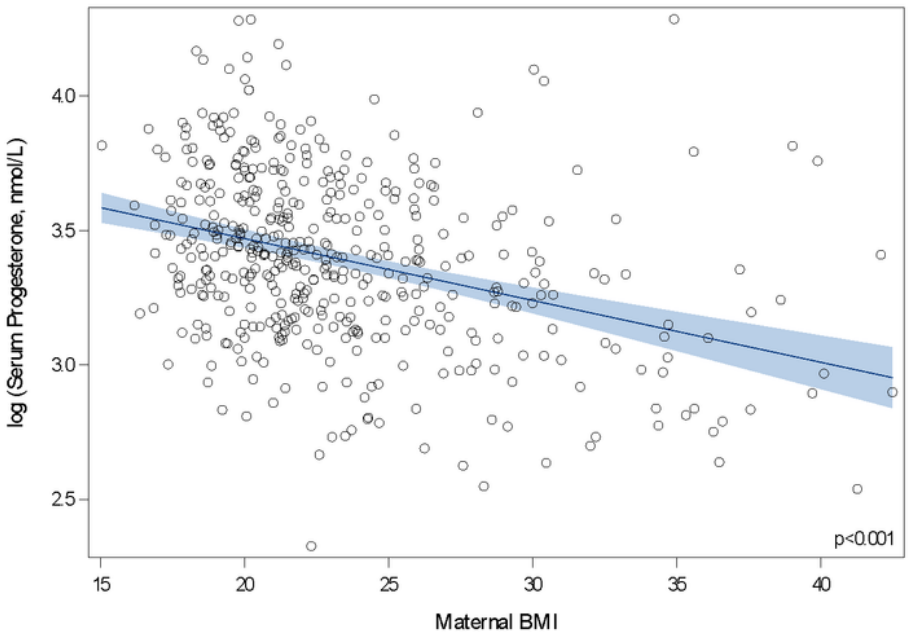

Figure 3

Relationship between maternal BMI and log serum progesterone levels, adjusted for gestation age, maternal age, parity and fetal gender.

Supplementary Files

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